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Head and Neck Cancers

Meta-Analysis on Induction Chemotherapy in Locally Advanced Nasopharyngeal Carcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Induction chemotherapy • Concurrent chemoradiotherapy • Nasopharyngeal carcinoma • Systematic review • Meta-analysis

Abstract

Purpose. Concurrent chemo radiotherapy (CCRT) has been the standard of care in locally advanced nasopharyngeal carcinoma (LA-NPC) for many years. The role of induction chemotherapy (ICT) has always been controversial. This systematic review and meta-analysis investigates the value of adding ICT to CCRT in LA-NPC.

Materials and Methods. Two reviewers independently assessed the eligibility of randomized controlled trials (RCTs) comparing ICT followed by CCRT versus CCRT alone, including treatment-naive adult patients with histologically proven nonmetastatic LA-NPC.

Results. Eight RCTs with in total 2,384 randomized patients, of whom 69% had N2–N3 disease, were selected. ICT was the allocated treatment in 1,200 patients, of whom 1,161 actually received this. Treatment compliance varied, with a median rate of 92% (range, 86%–100%) of patients receiving all cycles of ICT. The percentage of patients completing radiotherapy was 96% and 95% [(Combined Risk difference(CRD)= 0.004; 95% Confidence Interval (CI) –0.001–0.01; $p = 0.14$)] in the ICT group and CCRT group, respectively, whereas chemotherapy during radiotherapy could be completed in only 28% of the ICT group versus 61% in the CCRT group (CRD, −0.243; 95% CI, −0.403 to −0.083; $p = .003$). Grade 3–4 acute toxicity was mostly hematologic during the ICT phase (496 events vs. 191 nonhematologic) and was predominant in the ICT group (1,596 events vs. 1,073 in the CCRT alone group) during the CCRT. Adding ICT to CCRT provided a significant benefit in overall survival (hazard ratio [HR], 0.680; 95% CI, 0.511–0.905; $p = .001$) and progression-free survival (HR, 0.657; 95% CI, 0.568–0.760; $p < .001$).

Conclusion. Although ICT followed by CCRT is associated with more acute toxicity and a lower compliance of the chemotherapy during the CCRT phase, this association resulted in a clinically meaningful survival benefit. ICT should be considered as a standard option in patients with LA-NPC, but further study on optimal patient selection for this treatment is warranted. ***The Oncologist*** 2021;26:e130–e141

Implications for Practice: Locally advanced nasopharyngeal carcinoma (LA-NPC) is a relatively common disease in some parts of the world, with a rather poor prognosis due to its high metastatic potential. The role of induction chemotherapy (ICT) has always been controversial. This meta-analysis found that ICT followed by concurrent chemoradiotherapy (CCRT) in LA-NPC is associated with a significant clinical improvement in both overall survival and progression-free survival compared with CCRT alone. ICT should be considered as a standard option in patients with LA-NPC.

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Introduction

Nasopharyngeal cancer (NPC) is a relatively rare entity in the world, with a unique, highly skewed geographical distribution, being very common in Southeast Asia, South China, North Africa, Micronesia, Polynesia, and Alaska [1]. It is a cancer that often evolves with low noise, explaining why more than 70% of NPCs are diagnosed in a locoregionally advanced (LA) stage [2]. A particular subtype, "undifferentiated carcinoma of nasopharyngeal type," is characterized by a better local tumor control but also by a greater propensity to metastasize [3]. This variety is also associated with an Epstein-Barr virus (EBV) latent infection [4]. NPC is one of the few head and neck cancers with very little place for surgery, with a management essentially based on radiotherapy (RT) with or without chemotherapy, concurrently and/or (neo)adjuvant [5]. NPC is radiosensitive and the therapeutic goal tends to be curative. However, the proximity of critical organs (brainstem, optic chiasm, optic nerves, brain, etc.) often bares a risk for late toxicity. In addition, reirradiation has become commonplace thanks to the development and diffusion of high precision techniques, both diagnostic and therapeutic. Therefore, RT is the cornerstone in NPC treatment, and modern radiation techniques and expert radiation oncologists are conditions for optimal results.

Localized NPC (T1–2, N0–1 Union for International Cancer Control [UICC]/American Joint Committee on Cancer [AJCC]) [6] has a favorable prognosis, with a local control rate of over 90%, obtained with exclusive RT [3]. However, with almost half of all patients presenting at an advanced stage, of whom one-third subsequently die as a result of this cancer within 5 years of diagnosis, whereby distant metastases are a key problem, the treatment of stage III to IVB NPC has been the main focus of clinical research in the past decades [5]. In that research, concurrent chemoradiotherapy (CCRT) has played a crucial role. The Intergroup-0099 study reported by Al-Sarraf et al. in 1998 was the first trial to achieve significant benefit in both progression-free survival (PFS) and overall survival (OS) when the combined approach of chemotherapy and RT was compared with RT alone [7]. In that study, use was made of both CCRT (cisplatin 100 mg/m^2 on days 1, 22, and 43 during RT) and adjuvant chemotherapy (3 cycles of cisplatin 80 mg/m^2 on day 1 and fluorouracil 1,000 mg/m^2 per day on days 1–4 post-RT). In retrospect, the suboptimal outcomes in the radiation alone arm can be (partially) attributed to the old radiation techniques used (two opposed lateral plus anterior supraclavicular field) in combination with a suboptimal delineation and dosimetry. In 2006, Baujat et al. published an individual patient-based meta-analysis of eight randomized trials and 1,753 patients with NPC, in which they studied the impact of adding chemotherapy to RT, given before (induction), or before and after (induction and adjuvant), or only during (concomitant) or during and after (concomitant and adjuvant) [8]. Adding chemotherapy to RT resulted in an absolute benefit in OS and event-free survival (EFS) at 5 years of 6% (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.71–0.95; p = .006) and 10% (HR, 0.76; 95% CI, 0.67–0.86; p = .00001), respectively. A significant interaction was observed between the timing of chemotherapy and OS (p = .005), which explained the heterogeneity observed in the treatment effect (p = .03), with the highest benefit resulting from concomitant chemotherapy. The role of induction chemotherapy (ICT) and adjuvant chemotherapy (AC) given alone or added to concomitant chemotherapy remained questionable. Therefore, that meta-analysis really pointed at the fact that concurrent CCRT was the cornerstone in the standard of care management of patients with LA-NPC.

In an updated analysis of this Meta-Analysis of Chemotherapy in Nasopharyngeal Collaborative Group, ICT plus CCRT ranked better than CCRT alone for PFS, locoregional control, and distant control [9]. The latter aspect is particularly of interest in those patients with the highest risk to develop distant metastases (T4 or N2–3) [10]. In addition, a meta-analysis including nine randomized clinical trials with 2,215 patients with LA-NPC confirmed that the addition of ICT to CCRT significantly improved PFS and OS versus CCRT with or without AC [11]. Finally, some more recent randomized phase III studies in patients with stages III–IVB (excluding T3–T4, N0 cases) nonkeratinizing NPC reported significant OS improvement with ICT-CCRT over CCRT alone, with acceptable toxicity [12–14].

For all these reasons, in the present article, we focus on the role of ICT in LA-NPC. For this, we conducted a systematic review of the literature followed by a meta-analysis of randomized controlled trials (RCTs) to determine the impact of adding ICT to CCRT on OS and PFS for patients with LA-NPC.

Materials and Methods

Selection Criteria

This meta-analysis brings together RCTs that include treatment-naive adult patients with histologically proven nonmetastatic LA-NPC. Only trials comparing ICT plus CCRT versus CCRT alone as curative treatment for LA-NPC were eligible. We excluded all trials reporting on AC and those not published in the English literature.

Search Strategy

We searched MEDLINE via PubMed and the Central Registry of Controlled Trials of the Cochrane Library for all RCTs comparing ICT plus CCRT versus CCRT alone in patients with LA-NPC. For this, the following equation was used: "('Nasopharyngeal Carcinoma' OR 'Nasopharyngeal Neoplasms') AND ('Randomized Controlled Trial') AND ('induction chemotherapy' OR 'neoadjuvant chemotherapy')". The final search date was on June 1, 2020. We also analyzed the published abstracts and the presentations made during the various conferences of renowned societies like the European Society for Medical Oncology, the European Society of Therapeutic Radiology and Oncology, the American Society for Therapeutic Radiology and Oncology, the American Society of Clinical Oncology and the Asian Clinical Oncology Society. We also consulted http://www.clinicaltrials.gov and http://www.who.int/trialsearch to spot ongoing studies.

Selection of Studies and Data Collection

Two reviewers (M.M and S.B.) independently identified potentially eligible articles and abstracts from the literature

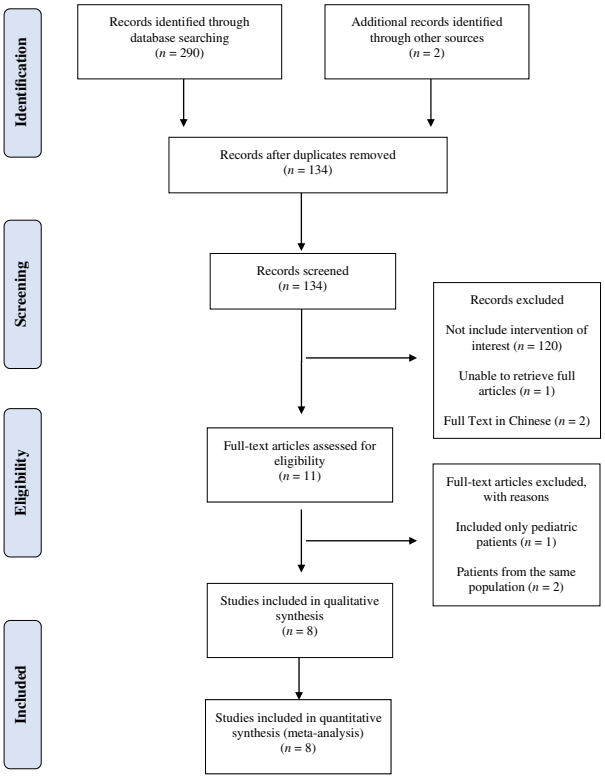

Figure 1. Flowchart of randomized controlled trial selection.

search. Results were compared and discussed between them. In case of discordance in the assessment of a study, a discussion decided on which RCTs to include in the meta-analysis. Then, the different data from the selected studies were extracted from the full publications by the same two reviewers and recorded in a database after consensus on the possible discrepancies. A final check on the extracted data was done by three other authors (M.P., J.B.V., D.V.G.).

Methodological Quality Assessment

Methodologically, the quality of the data reported in these studies was evaluated using the Oxford Quality Score (Jadad Score) [15].

Outcomes and Statistical Analysis

OS, PFS, and side effects were chosen as outcomes for this meta-analysis. For the two time-to-event endpoints (OS and PFS), we extracted from the individual trials the HR as treatment effect using the CCRT arm as a reference. If the estimated HR and its variance were directly available in an individual trial, then these values were used; in case of unavailability of this information, we planned to extract the statistical results of each trial according to the method detailed by Parmar et al. [16], allowing us to extrapolate the estimated HR and its variance. The individual HR point estimates were combined (in case of the null hypothesis of the homogeneity of the treatment effect) across the various trials, using the fixed-effects Peto method [17]. By convention (as CCRT arms of individual trials were used as reference), an overall HR <1 implied a benefit for the ICT arm. In case of a significant test for heterogeneity (p = .10) using a Q statistic, a random-effects method was applied [18]. To address the occurrence of adverse events (≥grade 3) and therapeutic compliance, we used as measure of treatment effect the risk difference (RD) (the proportion of the event of interest in the ICT arm minus the proportion of the event in the CCRT arm). RDs were combined using the Dersimonian and Laird method in case of detectable heterogeneity between studies [19]. Otherwise, a fixed-effects method was applied using the inverse of the individual variance as weight for calculating an average treatment effect. Forest plots were generated using DistillerSR Forest Plot Generator from Evidence Partners.

Results

Characteristics of Included Trials

The flowchart of the RCT selection can be found in Figure 1. Out of 292 studies identified by our search, 8 RCTs [13, 14, 20–25] were included in our meta-analysis, accounting for 2,384 randomized patients, of whom 1,200 and 1,184 were assigned to receive ICT plus CCRT and CCRT, respectively. The quality assessment and the characteristics of the trials are summarized in Tables 1 and 2. The study population was relatively young, with a median age between 42 and 50 years and between 42 and 52 years in the ICT plus CCRT group and the CCRT alone group, respectively (Table 2). These patients were also in good general condition at the time of their randomization, with nearly all (2382/2384) patients having an Eastern Cooperative Oncology Group performance status (PS) ≤1 or a Karnofsky Index ≥70, whereas only two patients had a PS of 2 (Table 2) [21].

The percentage of T4 and N2–N3 disease was 43% and 69%, respectively. Six out of eight trials included only stages III–IVB [13, 14, 20, 22, 24, 25], and the remaining two trials also included stage IIB [21, 23]. In five trials, there were only World Health Organization type II and type III NPCs included [13, 14, 22, 23, 25]; two trials [21, 24] had also included type I NPC, and in the remaining trial [20], the histological type was not specified (Table 2).

Therapeutic treatment regimens

The ICT regimens, although diverse and varied, were all platinum-based, using cisplatin in seven trials [13, 14, 20, 21, 23–25] and carboplatin in one trial (Table 2) [22]. ICT consisted of a triple regimen in four trials (37% of all ICT patients) [13, 21–23], with docetaxel, cisplatin, and 5-fluorouracil regimen in two trials (24%) [13, 23]; doublets in three trials [14, 20, 25] (43%); and a regimen with five different drugs applied in one trial (20%; Table 2) [24]. All trials used cisplatin during the CCRT phase: five [20–24] at a weekly low dose (30–40 mg/m^2 delivered over 7 to 8 weeks) and three [13, 14, 25] at a 3-weekly high dose (80–100 mg/m^2 and planned for 3 cycles during radiation; Tables 2, 3). Intensity modulated radiotherapy (IMRT) was used in all patients in only two trials [13, 14]; in the other six trials [20–25], some patients were treated with non-IMRT techniques such as two-dimensional or three-dimensional RT (Table 2).

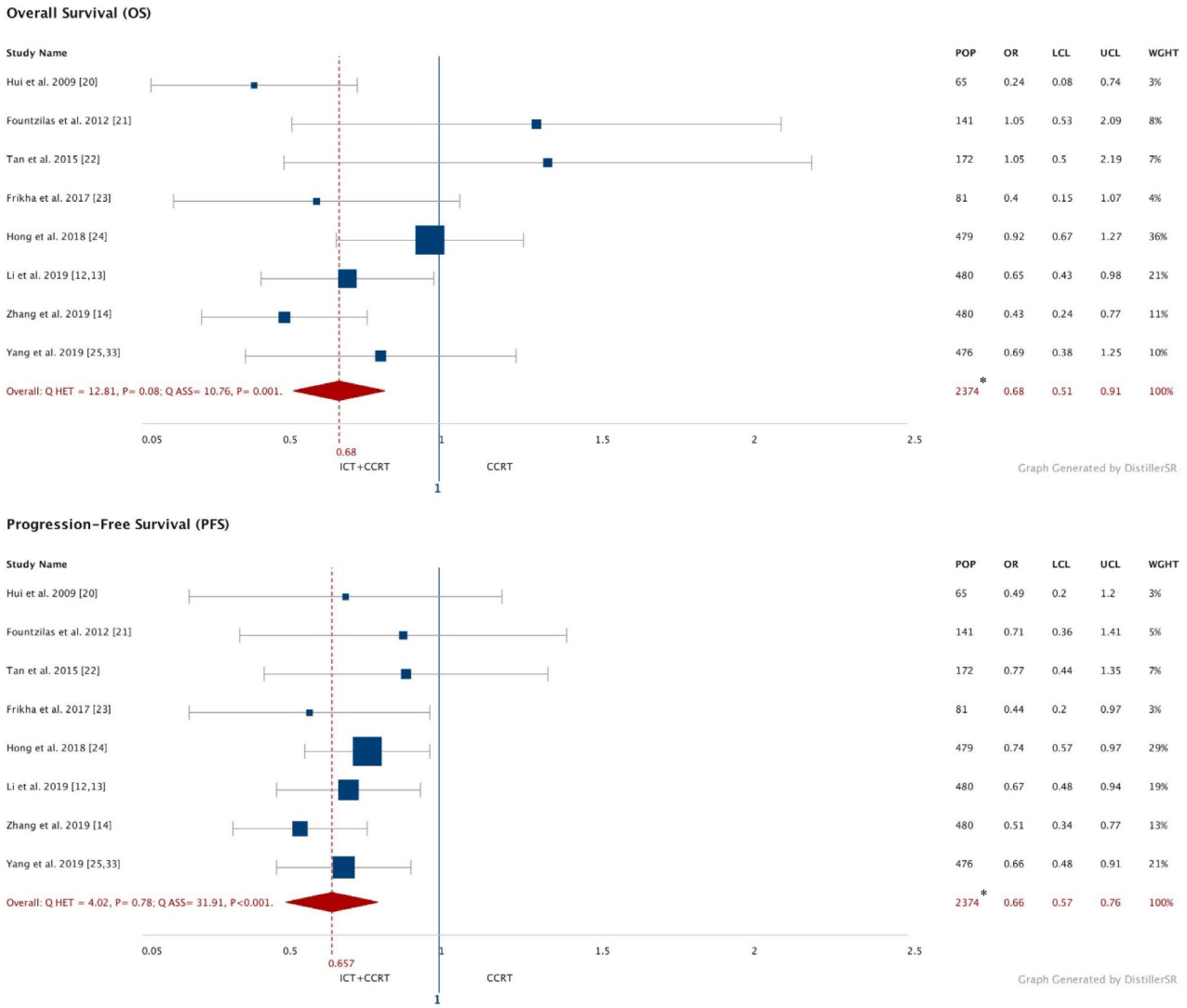

Figure 2. Forest plots of hazard ratio (HR) for overall survival and progression-free survival. The estimated HR for each individual trial is indicated by the center of the square, and the horizontal line gives the 95% confidence interval (CI). The closed diamonds shows overall HR and its 95% CI. HR <1 and 95% CI excluding 1 indicate improved overall survival and progression-free survival for ICT plus CCRT versus CCRT.
Abbreviations: *, analysis were performed on 2374 (/2384) patients. Ten patients were excluded by the initial authors (6 [IC+CCRT] + 2 [CCRT] by Tan et al. and 2 [IC+CCRT] by Frikha et al.). ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; LCL, lower confidence limit; OR, odds ratio; POP, population; Q ASS, Q-Test of Association; Q HET, Q-Test of Heterogeneity; UCL, upper confidence limit; WGHT, weight.

Treatment compliance

Treatment compliance during the ICT phase was good, resulting in a median rate of 92% (range, 86%–100%) of patients receiving all planned cycles (Table 3). As can be seen in Table 3, compliance to RT during the CCRT phase was very good as well. Only in the study of Hong et al. [24] were these data not available. The percentage of patients completing RT in the seven evaluable trials was 96% and 95% in the ICT plus CCRT group and the CCRT alone group, respectively (CRD, 0.004; 0.95% CI, −0.001 to 0.01; p = .14) [13, 14, 20–23, 25]. Also, the mean or median number of days of RT, reported only in four studies, did not show a negative influence of adding ICT to CCRT and were quite comparable between both groups [20–23]. However, compliance to the concomitant chemotherapy was generally poor, with a significant difference in favor of the CCRT alone arm (61% vs. 28% completing all concomitant chemotherapy cycles; CRD, −0.243; 95% CI, −0.403 to −0.083; p = .003) [13, 14, 20–23, 25]. Compared with the 3-weekly regimens, compliance to the weekly regimens seemed artificially low if one simply looked at how many patients actually received the planned eighth cycle. As an example, only 0%–3% in the two arms of the study of Hui et al. did receive the eighth cycle [20]. However, the percentage of patients who received a cumulative cisplatin dose of 200 mg/m^2 or more in that study was estimated to be much higher (i.e. 74% in the ICT arm and 76% in the CCRT alone arm, and 63% and 81% for the three studies on the weekly regimen) [20–22], enabling the calculation of this parameter (see Table 3). For the three trials combined using the high-

Table 1. Quality assessment of all eight included trials

Author	Jadad score					Loss to FU	ITT	PP	Sample size	Allocation concealment	Primary endpoint[a]
	Rand.	Blinding	Withdrawals	Description of rand.	Total score						
Hui et al. 2009 [20]	1	0	1	1	3	No	Yes	Yes	Yes	No	Toxicity
Fountzilas et al. 2012 [21]	1	0	1	1	3	Yes	Yes	No	Yes	No	Objective response
Tan et al. 2015 [22]	1	0	1	1	3	No	No	Yes	Yes	No	Overall survival
Frikha et al. 2017 [23]	1	0	1	1	3	Yes	No	Yes	Yes	Yes	Progression-free survival
Hong et al. 2018 [24]	1	0	1	1	3	Yes	Yes	No	Yes	No	Progression-free survival
Li et al. 2019 [12, 13]	1	0	1	1	3	Yes	Yes	No	Yes	Yes	Failure-free survival
Zhang et al. 2019 [14]	1	0	1	1	3	No	Yes	Yes	Yes	Yes	Recurrence-free survival
Yang et al. 2019 [25, 34]	1	0	1	1	3	Yes	Yes	No	Yes	Yes	Disease-free survival

Abbreviations: FU, follow-up; ITT, intention to treat; PP, per protocol; Rand., randomization.
[a]As defined in the original publications

dose 3-weekly cisplatin regimen [13, 14, 25] the percentage of patients that was able to receive three cycles was 31% in the ICT arm and 67% in the CCRT alone arm (supplemental online Appendix 2). A cumulative dose of ≥200 mg/m^2 was reached in 63% of the patients in the ICT arms and 88%in the CCRT alone arms (Table 3, supplemental online Appendix 2).

Toxicity and Quality of Life Scoring

We found a large variation in the reporting of acute and late toxicity, including different grading systems. Among the eight RCTs, four different toxicity grading systems were used: CTCAE (versions 2.0–4.0) was applied in all RCTs; Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG) in six RCTs [13, 14, 20, 22, 24, 25]; RTOG Acute Radiation Morbidity Scoring Criteria in two RCTs [21, 22], and European Organisation for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring schema also in two RCTs [20, 24]. In total, four RCTs [20–22, 24] used three different grading scales, three RCTs [13, 14, 25] used two, and one RCT [23] used only one (CTCAE, version 3). Four RCTs [20, 21, 23, 25] did not report grade 1–2 toxicities; all eight reported late toxicities, but not in a homogeneous way. Acute grade 5 toxicity, reported on by all, was seen in five RCTs [13, 21, 22, 24, 25], four patients (0.3%) in the ICT plus CCRT group versus six (0.5%) in the CCRT alone group. In addition, only two RCTs [20, 22] reported data on quality of life using the EORTC algorithm QLQ-30 version 3.0 and QLQ-H&N35. Because of lack of precision in reporting of some acute toxicity data, one trial had to be excluded from the toxicity analysis during the ICT phase [13] and one during the CCRT phase [23]. Grades 3–4 acute toxicity during the ICT phase was essentially hematologic (496 events vs. 191 nonhematologic), with leucopenia and neutropenia being the most frequent ones (Table 4). The nonhematologic toxicity during ICT is depicted in Table 4.

During the CCRT phase, grades 3 and 4 acute toxicities were clearly predominant in the ICT plus CCRT group (1,596 events vs. 1,073 in the CCRT alone group; supplemental online supplemental online Appendix 1). Overall, of the 2,669 grade 3–4 acute adverse events reported, 1,128 were hematologic and 1,541 were nonhematologic (supplemental online Appendix 1). These toxicities were observed clearly more often in the ICT plus CCRT group compared with CCRT alone group. This was particularly the case for hematologic toxicity (30% vs. 12% of all events) and to a lesser extent for the nonhematologic toxicity (30% vs. 28%). Leucopenia (CRD, 0.106; 95% CI, 0.029–0.184; p = .007), thrombocytopenia (CRD, 0.110; 95% CI, 0.040–0.180; p = .002), and anemia (CRD, 0.041; 95% CI, 0.002–0.079; p = .04) were all higher in the ICT + CCRT arm.

The lack and heterogeneity of data did not allow for an accurate analysis of late side effects.

Therapeutic Efficacy

Overall, ICT followed by CCRT provided a significant benefit in outcomes compared with CCRT alone, both for OS (HR, 0.680; 95% CI, 0.511–0.905; p = .001) and for PFS (HR, 0.657; 95% CI, 0.568–0.760; p < .001) (Figure 2). This

Table 2. Description of the eight included trials

Trial	Trial Phase	Randomized patients, *n*			KPS ≥ 70 or PS ≤ 1, %	Median age		Median FU, yr	WHO type	T4 stage *n* (%)	N2-N3 stage *n* (%)	Stage	RT technique	RT dose fractionation regimen	ICT regimen	Dose of CDDP during RT	Rating, PFS and OS, yr	PFS ICT + CCRT/ CCRT, %	OS, ICT + CCRT/ CCRT, %
		Total	ICT + CCRT/ CCRT			ICT + CCRT/ CCRT, yr													
Hui et al. 2009 [20]	II	65	34	31	100	50	45	4.3	NR	14 (22)	41 (63)	III–IVB (AJCC 5th)	IMRT 2D-RT (Ho's technique)	66–86Gy/33–43 fx; 2 Gy/fx per d; 8.6 wk +18 Gy brachyboost if persistent tumor at 6 wk	CDDP 75mg/m^2 (d1), docetaxel 75mg/m^2 (d1) (2*q3wk)	40 mg/m^2 per wk (8 wk)	3	88.2/59.5	94.1/67.7
Fountzilas et al. 2012 [21]	II	141	72	69	99	49	51	4.6	I–III	37(26)	86 (61)	IIB–IVB (AJCC 6th)	3D-RT, 2D-RT	66–70 Gy/33–35 fx, 6.5–7 wk	CDDP 75mg/m^2 (d2); paclitaxel 175mg/m^2 (d1); epirubicin 75mg/m^2 (d1) (3*q3wk)	40 mg/m^2 per wk (8 wk)	3	64.5/63.5	66.6/71.8
Tan et al. 2015 [22]	II-III	180	92	88	100	48.5	51.6	3.4 (IC+CCRT); 3.2 (CCRT)	II–III	37 (22)	143 (83)	III–IVB (AJCC 5th)	IMRT, 2D-RT (modified Ho's technique)	*IMRT: 69.96 Gy/33 fx; 2.12 Gy/fx per d; 6.6 wk; *2D-RT: 70 Gy/35 fx; 2 Gy/fx per d; 7 wk	Carboplatin AUC 2.5; gemcitabin 1000mg/m^2; paclitaxel 70 mg/m^2 (d1 and d8) (3*q3wk)	40 mg/m^2 per wk (8 wk)	3	74.9/67.4	94.3/92.3
Frikha et al. 2017 [23]	III	83	42	41	100	46*	48*	3.6	II–III	29 (36)	51 (63)	IIB–IVB (AJCC 6th)	IMRT; non-IMRT	70 Gy/35 fx	CDDP 75mg/m^2 (d1); docetaxel 75mg/m^2 (d1); 5FU 750mg/m^2 (d1 to d5) (3*q3wk)	40 mg/m^2/wk (7 wk)	3	73.9/57.2	86.3/68.9
Hong et al. 2018 [24]	III	479	239	240	100	45	47	6.0	I–IIb	344 (72)	403 (84)	IVA–IVB (AJCC 5th)	IMRT; 3D-RT	≥70 Gy; 1.8–2.2 Gy/fx per d; 5 fx/wk	Mitomycin 8mg/m^2 (d1); epirubicin 60mg/m^2 (d1); CDDP 60mg/m^2 (d1); 5FU 450 mg/m^2 (d8); leucovorin 30 mg/m^2 (d8) (3*q3wk)	30 mg/m^2 per wk (7 wk)	5	61/50	72/68
Li et al. 2019 [12, 13]	III	480	241	239	100	42	44	6.0	II–III	180 (38)	276 (58)	III–IVB (except T3–4N0) (AJCC 7th)	IMRT	66–74Gy; 2.0–2.35 Gy/fx per d; 5fx/wk; 6–7 wk	CDDP 60mg/m^2 (d1); docetaxel 60mg/m^2 (d1); 5FU 600mg/m^2 (d1–d5) (3*q3wk)	100 mg/m^2 (3*q3wk)	5	77.4/66.4	85.6/77.7
Zhang et al. 2019 [14]	III	480	242	238	100	46	45	3.6	II–III	212 (44)	260 (54)	III–IVB (except bulky primary tumor N0) (AJCC 7th)	IMRT	66–70 Gy; 30–33 fx	Gemcitabin 1000mg/m^2 (d1 and d8); CDDP 80mg/m^2 (d1) (3*q3wk)	100 mg/m^2 (3*q3wk)	3	85.3/76.5	94.6/90.3
Yang et al. 2019 [25, 33]	III	476	238	238	100	44	42	6.9	II–III	164 (34)	382 (80)	III–IVB (except T3N0–1) (AJCC 6th)	IMRT; 2D-RT	*IMRT: ≥66Gy 2–2.33 Gy/fx per d; *2D-RT: 64–72 Gy; 2 Gy/fx per d; 5 fx/wk	CDDP 80mg/m^2 (d1); 5FU 800mg/m^2; (d1 to d5) (2*q3wk)	80 mg/m^2 (3*q3wk)	5	73.4/63.1	80.8/76.8

Abbreviations: 2*q3wk, 2 cyles every 3 weeks; 2D, two-dimensional; 3*q3wk, 3 cycles every 3 weeks; 5FU, 5-fluorouracil; AJCC, American Joint Committee on Cancer; AUC, area under the curve; CDDP, cisplatin; ICT, induction chemotherapy; IMRT, Intensity Modulated Radiotherapy; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

Table 3. Compliance to treatment

				Concurrent chemoradiation (calculated on number starting RT)								
					Radiotherapy			Chemotherapy				
Trial	Arm	*n*[a]	ICT completed, calculated on ITT, %	*n*[b]	Completed, %	Duration, d	Total dose, Gray	Weekly or 3-weekly	Planned dose/cycle, mg/m^2	Planned number of cycles	% pts receiving dose as planned	% pts with ≥ 200 mg/m^2 cumulative cisplatin dose
Hui et al. 2009 [20]	ICT+CCRT	34	100	34	100	58.8[c]	78.4[c]	Weekly	40	8	3	74[d]
	CCRT	31		26	100	56.6[c]	76.5[c]	Weekly	40	8	0	76[d]
Fountzilas et al. 2012 [21]	ICT+CCRT	72	86	65	94	51.8[e]	70[e]	Weekly	40	8	8	58
	CCRT	69		68	94	51.1[e]	70[e]	Weekly	40	8	9	75
Tan et al. 2015 [22]	ICT+CCRT	92	86[f]	86	100	NR	NR	Weekly	40	8	26	61[d]
	CCRT	88		86	99	NR	NR	Weekly	40	8	42	72[d]
Frikha et al. 2017 [23]	ICT+CCRT	42	93[f]	41	83	53.1[c]	NR	Weekly	40	7	32	NR
	CCRT	41		40	90	51.8[c]	NR	Weekly	40	7	55	NR
Hong et al. 2018 [24]	ICT+CCRT	239	95	232	NR	NR	NR	Weekly	30	7	26	NR
	CCRT	240		227	NR	NR	NR	Weekly	30	7	73	NR
Li et al. 2019 [12,13]	ICT+CCRT	241	88	238	100	46[e,g]	70[e]	3-weekly	100	3	31	86
	CCRT	239		238	99	46[e,g]	70[e]	3-weekly	100	3	56	98
Zhang et al. 2019 [14]	ICT+CCRT	242	96	239	100	NR	NR	3-weekly	100	3	39	80
	CCRT	238		237	99	NR	NR	3-weekly	100	3	75	96
Yang et al. 2019 [25,33]	ICT+CCRT	238	91	219	100	NR	NR	3-weekly	80	3	23	23
	CCRT	238		214	100	NR	NR	3-weekly	80	3	71	71

[a]Refers to number of patients randomized.
[b]refers to number of patients who started RT.
[c]Mean.
[d]Educated estimate.
[e]Median.
[f]Recalculated on the intent to treat population.
[g]Data retrieved from Sun et al. [12].
Abbreviations: CCRT, concurrent chemo radiotherapy; ICT, induction chemotherapy; ITT, intention to treat; NR, not reported; pts, patients; RT, radiotherapy.

Table 4. Hematologic and nonhematologic acute adverse events grade 3–4 during induction chemotherapy according to patients who started it

Trial[a] grade ≥ 3 acute toxicity	Hui et al. 2009 [20], *n* = 34	Fountzilas et al.2012 [21], *n* = 66	Tan et al. 2015 [22], *n* = 86	Frikha et al. 2017 [23], *n* = 41	Hong et al. 2018 [24], *n* = 237	Zhang et al. 2019 [14], *n* = 239	Yang et al. 2019 [25, 33], *n* = 219	Grade 3–4 adverse events, *n* (%)	No. of pts. evaluated per toxicity
Hematologic									
Leukopenia	NR	0	16	NR	139	26	12	193 (23)	847
Neutropenia	33	6	50	11	NR	49	35	184 (27)	685
Febrile neutropenia	4	0	NR	3	10	0	NR	17 (3)	617
Thrombocytopenia	0	0	0	NR	66	13	0	79 (9)	881
Anemia	0	1	1	NR	16	4	1	23 (3)	881
Total	37	7	67	14	231	92	48	496	
Nonhematologic									
Vomiting, nausea, anorexia	3	4	0	NR	42	48	10	107 (12)	881
Diarrhea	NR	0	NR	NR	NR	1	1	2 (0.4)	524
Mucositis, dysphagia, odynophagia	0	0	NR	5	3	2	3	13 (2)	836
Fatigue	2	1	0	4	NR	NR	NR	7 (3)	227
Allergic reaction	NR	1	1	NR	NR	1	1	4 (1)	610
Hepatotoxicity	NR	0	2	NR	4	5	2	13 (2)	847
Nephrotoxicity	NR	0	NR	NR	0	3	0	3 (0.4)	795
Weight loss	NR	0	NR	NR	NR	0	0	0 (0)	524
Alopecia	NR	36	0	6	NR	NR	NR	42 (22)	193
Total	5	42	3	15	49	60	17	191	

[a]The study from Li et al. [12, 13] was excluded as they did not report on toxicity during the induction chemotherapy phase.
NR, not reported.

benefit of ICT is independent of the concurrent CDDP schedule (interaction test 3-weekly vs. weekly: $p = 0.40$ for OS; $p = 0.28$ for PFS).

There was evidence of heterogeneity between trials for OS (Q = 12.810; $p = .08$) but not for PFS (Q = 4.022; $p = .78$) (Figure 2). In all studies, OS was defined as the time from randomization to death from any cause, and PFS was defined as the time from randomization to disease recurrence or death from any cause. The sensitivity analysis demonstrated that no single trial exerted a significant influence on the overall result (OS and PFS). A fixed-effects model is reported for PFS, whereas a random-effects model was applied for OS. OS, PFS, and side effects were the primary or secondary endpoints reported in these trials. Very little information on locoregional and distant control rates was available in the publications; therefore, we do not report any result on those outcomes.

Discussion

Following the landmark Intergroup 0099 (INT-0099) trial, various randomized studies and meta-analyses have confirmed the benefit of adding concomitant chemotherapy to RT in patients with NPC, in terms of both locoregional control and in distant control [8, 9, 26, 27]. However, even with "optimal" CCRT, outcome of LA-NPC remains poor, in particular because of the high risk of metastatic spread. Further treatment intensification by adding chemotherapy to standard CCRT, whether in the induction setting and/or in the adjuvant setting, could therefore be of interest to study. As such, ICT offers some advantages over AC for improved tolerance and early eradication of micrometastases [12]. Moreover, as known from large primary tumors abutting or infiltrating critical structures, the use of ICT can be used to shrink the tumor bulk for better dose coverage during subsequent CCRT [5]. In a broader sense, this last issue is especially of relevance as the regional anatomy of the nasopharynx is extremely complex with NPC lying in close vicinity to vital, radiosensitive organs (brain, brainstem, optic chiasm, optic nerves, eyes, etc.) and with complicated patterns of local and regional spread. Finally, as in some NPC endemic countries access to radiation therapy can be very difficult with very long waiting times, ICT allows the NPC patient to be treated effectively while waiting for CCRT.

The first individual patient-based meta-analysis of Baujat et al., including only eight trials and 1,753 patients, showed an OS benefit related to CCRT, but not related to ICT, despite it had a positive effect on EFS [8]. An excess in treatment-related death during ICT might have been guilty of that, which made the authors even suggest that better management of the adverse events could allow ICT to play a role in the treatment of LA-NPC [8].

More recently, Tan et al. performed a meta-analysis of 11 trials and 2,802 patients with LA-NPC to compare the effects of ICT followed by CCRT versus CCRT alone, on OS, PFS, distant metastasis-free survival, and adverse events [28]. The particularity of this meta-analysis was that it included both RCTs and observational studies. The proportion of patients with stage IV disease ranged from 40% to 47% in the RCTs and from 37% to 59% in the observational studies. Overall, the addition of ICT showed to improve both PFS and OS. Further analysis revealed that the risk of death was reduced both in the RCTs (risk reduction [RR], 23%; HR, 0.77; 95% CI, 0.60–0.98, $p = .03$) and in the observational studies (RR, 42%; HR, 0.58; 95% CI, 0.39–0.89, $p = .01$). However, this improvement in OS was achieved at the cost of an increase in adverse events. Late toxicity was not adequately reported in most studies and treatment compliance was not discussed.

Huge variation in toxicity reporting was also found in the eight RCTs included in our analysis, with only very few data on late toxicity compared with acute toxicity and the impossibility to separate grade 3 from grade 4 toxicity. This made it impossible for us to draw any firm conclusion on the impact of ICT on the occurrence of late toxicity beyond what could be expected from CCRT alone. Publications and studies specifically focusing on late toxicity in patients with NPC, as has been done in head and neck squamous cell cancer [29, 30], are lacking and therefore an unmet need. Moreover, such data would be helpful in deciding what regimens are preferable to use. Like in Tan's meta-analysis, we found ICT to be associated with more acute grades 3–4 toxicity during the CCRT phase compared with that observed in the CCRT alone arms (especially more hematologic toxicities). This excess of acute toxicity during CCRT when using ICT had a negative influence on the chemotherapy compliance during CCRT but not on RT compliance. In fact, chemotherapy compliance during the CCRT phase was significantly worse in the ICT arms compared with that observed in the CCRT alone arms (only 28% of patients completed all concurrent chemotherapy cycles vs. 61% in the CCRT group; CRD, −0.243; 95% CI −0.403 to −0.083; $p = .003$), but evidently this had no negative effect on therapeutic outcome. Regarding the concurrent chemotherapy schema, data on the compliance in the weekly low-dose versus 3-weekly high-dose cisplatin-based scheme are heterogeneous and frequently lacking, which makes it impossible to draw any firm conclusions. As an example, the largest study on the weekly scheme, by Hong et al. ($n = 479$), reported 90% and 51% completing the seventh cycle in the experimental and control group, respectively. These numbers are counterintuitive but are completely understandable if one knows that the relative dose intensity of their 30 mg/mg^2 per week scheme was 11% and 54% in the seventh week, resulting in a more logical weekly mean dose of 19 and 26 mg/mg^2 in the experimental and control group, respectively.

Therapeutic compliance is also of interest when comparing the role of ICT versus AC in relation to CCRT in patients with NPC. The earlier mentioned landmark Intergroup 0099 trial of Al-Sarraf et al. [7] randomized 193 patients with stages III and IV NPC to be treated with RT alone or CCRT with cisplatin, followed by three cycles of cisplatin plus infusional fluorouracil. OS was superior with the combined arm (3-year OS, 78% vs. 47% with RT alone; HR, 2.5; 95% CI, 1.29–4.84, $p = .005$). However, in terms of therapeutic compliance, only 63% of patients were able to receive three courses of high-dose cisplatin during CCRT, and only 55% could complete the three cycles of AC after the CCRT. Wee

et al [31], using a similar design as the Intergroup 0099 study, also reported a significant benefit associated with the addition of chemotherapy, although again, as in the Intergroup study, the contribution of the AC itself toward the survival improvement remained uncertain. However, again, the treatment compliance was problematic. The investigators noted that of the 111 patients in the CCRT arm, 46 patients (41%) had protocol deviations during the CCRT phase, including 5 patients who declined all cycles of chemotherapy; and 74 patients (67%) had treatment deviations during the AC phase, of whom 38 received no chemotherapy at all [31]. This low therapeutic compliance during AC was also observed in the RCT in patients with LA-NPC reported by Chan et al. [32]. This study compared RT preceded and followed by chemotherapy versus RT alone. All patients in the chemo-RT arm were able to complete both ICT and RT as preplanned in the protocol. However, during the adjuvant phase, two patients (5.4%) refused to complete chemotherapy, and 15 patients (40.5%) had cessation of chemotherapy before completion, because of grade 3 hematologic toxicity [32]. The high compliance during ICT was also confirmed in the studies of our meta-analysis in which a median of 92% of patients completed all cycles of ICT as per protocol.

Two other meta-analyses have to be mentioned here that looked at potential preference of ICT versus AC. Wang et al. [11] reported in 2016 on a meta-analysis of nine randomized trials and 2,215 patients with LA-NPC, in which they compared the efficacy and safety of ICT followed by CCRT versus CCRT with or without AC. In this meta-analysis, ICT had a favorable outcome inducing a significant improvement in PFS (HR, 0.68; 95% CI, 0.56–0.81; p = .001) and OS (HR, 0.64; 95% CI, 0.49–0.84; p = .001) compared with CCRT with or without AC. However, this improvement in outcome was at the cost of an increased risk of acute grade 3–4 anemia, thrombocytopenia, leucopenia, and fatigue [11]. The most recent update of the individual patient-based meta-analysis included data of 20 RCTs and 5,144 patients comprised most randomized trials conducted up to December 31, 2010, and had a median follow-up of 7.4 years [9]. Therefore, this meta-analysis did not include the more recently published randomized phase III trials, comparing ICT followed by CCRT versus CCRT alone. This network meta-analysis evaluated the benefit of adding chemotherapy (CT) to RT in patients with nonmetastatic NPC (49% stage III, 42% stage IV). The authors concluded that (a) schedules containing CCRT most often ranked better than schedules without CCRT; (b) when focusing on schedules containing CCRT, the ones with the addition of AC always ranked better than CCRT alone, although the differences in head-to-head comparison were only significant for PFS and locoregional control, whereas ICT added to CCRT ranked better than CCRT for PFS, locoregional control, and distant control; and (c) schedules containing more than one timing of CT generally resulted in more toxicity than the use of only one timing but did not formally perform a direct comparison between different timing of CT [9]. Their meta-analysis did not take into account nor discussed therapeutic compliance, which in our opinion seems to favor ICT. Furthermore, as treatment failure nowadays mainly concerns distant failure and contemporary ICT regimens are more efficacious, the role of ICT will come forward more strongly. This is also evident from our meta-analysis, which includes these more recent trials on ICT.

At this moment, neither the optimal ICT regimen nor the dose schedule of the cisplatin during CCRT has been established. Nevertheless, we believe that our data strongly support the benefit of ICT-CCRT. The choice of the most suited IC regimen for a given patient must be based on clinical judgment, evaluation of the risk of local and distant relapse, and discussion with the patient about the potential risks and benefits of the different treatment. Although we are aware of the ongoing controversy on using weekly low-dose versus 3-weekly high-dose cisplatin during radiation, we could not find any argument in favor of one of the two regimens. The major limitation of our study is to define with certainty a poor prognosis group who might benefit most from treatment intensification (i.e., using ICT in addition to CCRT). Most recent trials that showed benefit of ICT included stage III to IVB NPC patients (except T3–4,N0; UICC/AJCC seventh edition), who were younger than 65 years, had a Karnofsky performance score of at least 70, and had adequate bone marrow, liver, and renal function. Although higher pretreatment EBV DNA levels are correlated with poor outcomes of patients with NPC, data on its application as a stratification factor and a selection tool for treatment intensification need further study [33].

Other limitations of our study need to be mentioned and concern the limited number of studies and highly selected young and fit patients included in the analysis, the fact that the analysis is based on published data and does not include individual patient data, the relatively short follow-up, with only three of the eight trials having a median follow-up of more than 6 years [13, 24, 25], and the inadequate information that could be retrieved from the involved studies with respect to late toxicities. In particular, this latter aspect will be of relevance in choosing the optimal ICT regimen for further studies.

Conclusion

Our meta-analysis clearly demonstrates that CCRT preceded by ICT in LA-NPC is associated with a significant and clinically meaningful improvement in both OS and PFS compared with CCRT alone; therefore, ICT followed by CCRT should be considered as a standard option in patients with LA-NPC. However, this benefit is at the cost of a higher acute grade ≥ 3 toxicity; therefore, further studies are needed to optimize this approach in order to make it as acceptable as possible for patients.

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Disclosures

Petr Szturz: Servier, Bristol-Myers Squibb (SAB); **Jan B. Vermorken:** Immunomedics, Innate Pharma, Merck-Serono, Merck Sharp & Dome Corp, PCI Biotech, Synthon Biopharmaceuticals, Debiopharm, Cue Biopharma, WntResearch (C/A), Merck-Serono, Merck Sharp & Dohme, Bristol-Myers Squibb (H); **Dirk Van Gestel:** Sanofi, Accuray, Merck-Pfizer, Takeda, Novartis (SAB, H). The other authors indicated no financial relationships.

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